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Attorney's Docket No.: 06275-188001 / D 1576-1P US

1617

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Tommy Ekstrom
Serial No. : 09/367,950
Filed : August 18, 1999
Title : NEW USE

Art Unit : 1617
Examiner : Jennifer M. Kim

Mail Stop Amendment
Commissioner for Patents
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REPLY TO ACTION OF MAY 4, 2004

In reply to the Office Action of May 4, 2004, Applicant submits the following remarks.

Claims 13-36, 38, and 42 are pending in the application.

The Examiner rejected claims 13, 35, 36, and 42 for lack of enablement under 35 U.S.C. §112, first paragraph, asserting that "the specification, while being enabling for the 'treatment of an acute episode of asthma,' does not reasonably provide enablement for the 'prevention of an acute episode of asthma'" (Office Action at page 2). Applicant strongly disagrees with the Examiner's assertion that prevention of acute episodes of asthma is not enabled.

Use of the claimed methods for both treatment and prevention is described explicitly in the specification. See, for example, page 1, lines 11-14 of the specification, which states: "The invention further relates to a method for prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma by administering, by inhalation, a composition..." (emphasis added). See also page 3, lines 21-27, which states:

> According to a further aspect of the invention a method of prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma, when needed, which comprises administering, by inhalation, to a patient an effective amount of a composition comprising, in admixture:
>
> (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate of such a salt; and
>
> (b) a second active ingredient which is budesonide. (emphasis added)

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The Examiner states that "[a]ll of the guidance provided by the specification is directed towards treatment rather than prevention of an acute episode of asthma" (page 4 of the Office Action). As demonstrated above, this is simply not true. Prevention (as opposed to treatment) of an acute attack is a simple matter of inhaling the composition of formoterol and budesonide before onset of the acute attack. This is amply taught by the specification, e.g., at page 3, lines 18-19: "We contemplate preventative use when the patient expects to encounter asthma inducing conditions, e.g., intends to take exercise or go into smoky conditions." When administered before the expected onset of an acute attack, the combination of formoterol (a bronchodilator) and budesonide (an anti-inflammatory agent) helps prevent the attack from occurring. Applicant is unsure why the Examiner believes that a patient would not be able to do this. Patients susceptible to asthma attacks induced by exercise, smoke or allergies are generally aware of this susceptibility and, if supplied with an appropriate medication, can self-administer it on an as-needed basis when they encounter conditions likely to trigger an attack, even before any symptoms occur. This is prevention.

The Office Action seems to imply that, because there are many different potential underlying causes of acute asthma attacks (e.g., different allergens), success in prevention of acute attacks would be unpredictable (Office Action at pages 3-4). Applicant notes that, regardless of the agent that triggers an asthma attack in a given patient, all such attacks appear to involve (1) inflammation of the airways, and (2) bronchoconstriction. Administering an anti-inflammatory agent (budesonide) simultaneously with a bronchodilatory agent (formoterol) prior to onset of such symptoms would prevent the symptoms from occurring; further, the increased use of the claimed combination during a period such as pollen season would effectively ensure sufficient budesonide is administered to act as a high level maintenance therapy, protecting the patient from exacerbations even at night during this especially risky period. This is discussed in the specification at page 4, lines 19-23. Applicant sees no rationale for the Examiner's position that prevention of acute asthma attacks is not enabled by the specification. The Examiner has cited no evidence that the claimed preventative therapy does not work. She is reminded that, absent such evidence, the assertions in Applicant's specification must be taken as true. In re

Marzocchi, 439 F.2d 220 (CCPA 1971). Furthermore, experimental evidence that treatment with the combination of formoterol and budesonide can prevent acute episodes of asthma was provided in the Declaration of Christer Hultquist submitted in the Response to Office Action dated December 10, 2002. Among the supportive evidence provided by Dr. Hultquist was a reference to Olsson et al. (ERS, Stockholm, 2002, poster P2451). This study showed that patients using the "on demand" treatment protocol suffered from fewer acute attacks than a control group on a fixed dose (see part 12 of the Declaration). This evidence and other evidence presented in the Declaration demonstrate that the methods described in the specification are indeed effective for the prevention of acute episodes of asthma. Applicant therefore respectfully requests that the rejection of the claims for lack of enablement be withdrawn.

Claims 13-15, 17, 18, 20-36, 38, and 42 were rejected under 35 U.S.C. 103(a) as being unpatentable over Carling et al., of record, in view of Tan et al. (1997). The Examiner points to various passages of Carling et al. that recite dosage regimens and compositions. As explained in previous responses, Carling et al. teaches that appropriate treatment dosages depend on the patient's age, weight, etc. (as the Examiner notes on page 6 of the Office Action). Carling et al. never suggests that a patient should vary the daily dosage of the medication based on the patient's symptoms, a limitation of the pending claims in the instant application. Further, as explained in the Declaration of Christer Hultquist, instructing a patient to do so would have been counter to accepted medical practice at the time of Applicant's invention. As explained in paragraph 6 of the Declaration, a patient prior to the present invention would have been instructed not to vary the dosage regimen without first consulting the patient's physician. If the patient experienced a change in symptoms, he would have had to arrange an appointment with his physician to discuss a change in the dosing regimen. Physicians generally do not instruct patients to take a medication "on demand" unless the medication is approved and labeled for such use.

The Examiner states that, according to Carling et al., a "patient experiencing acute asthmatic attack even with ongoing twice a day dosing regimen...can safely inhale additional

6 inhalations without going over the maximum suitable daily dosage..." (page 8 of the Office Action). The Examiner is mischaracterizing the teachings of Carling et al.

Carling et al. makes it clear that the administration should be twice per day, and says nothing whatsoever about additional administrations. See, for example, page 4, lines 19-21: "The combination according to present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma." See also page 6, lines 22-25: "The intended dose regimen is a twice daily administration, where the suitable daily dose of formoterol is in the range of 6 to 100 μg with a preferred dose of 6-48 μg..."

Applicant presumes that the Examiner's statement that a patient can "safely inhale additional 6 inhalations" is derived from the upper limit of 100 μg per day mentioned by Carling et al. at page 6, line 24, combined with the disclosure on pages 7-9 of some formulations that contain as little as 12 μg formoterol. No other basis for the Examiner's statement is apparent. Applicant submits that this is not an appropriate interpretation of Carling et al.'s teachings. Carling et al. says that the total daily dose can vary from 6 μg to 100 μg, and that the proper daily dose for a given patient "will strongly depend on the patient's age, weight, etc. and on the severity of the disease" (Carling et al. at page 6, lines 27-29). Thus, the physician would have considered factors such as age, weight and disease severity in selecting the fixed daily dose to prescribe for a given patient. For some patients this fixed daily dose may be as little as 6 μg/day, for others as much as 100 μg/day. Once a daily dose is selected, the patient (according to Carling et al.) will be instructed to split that total dose into two administrations per day. Contrary to the Examiner's assumption, there is no indication whatsoever in Carling et al. that a patient who has been prescribed, for example, two daily administrations of 12 μg each can "safely inhale additional 6 inhalations without going over the maximum suitable daily dosage." The maximum suitable daily dosage for a given patient varies by patient, and would have been taken into account by the patient's physician when the fixed twice-daily dose was prescribed. Nothing in Carling et al. teaches otherwise.

Tan et al. is cited as teaching that, "in acute asthma, systemic corticosteroid (e.g., budesonide) should be administered as soon as possible, in order to restore normal airway

β2-AR sensitivity, particularly in patients who are receiving regular long-acting β2-agonists (e.g., formoterol)" (Office Action at page 7). Applicant first notes that Tan et al. does not teach that budesonide is an example of a "systemic corticosteroid," and indeed it is not. Budesonide is a locally active corticosteroid, but once it enters the bloodstream it is rapidly inactivated in the liver (see, e.g., Carling et al.'s description of budesonide at page 2, lines 29-35). As a consequence, it exhibits little or no systemic activity. Note that Tan et al. tested oral prednisolone and intravenous hydrocortisone (two systemically active corticosteroids), and not oral or intravenous budesonide. Thus, the Examiner's characterization of Tan et al. as teaching systemic administration of budesonide "as soon as possible" in acute asthma is simply wrong. What Tan et al. does teach about budesonide is that inhaled (i.e., locally administered) budesonide is a standard daily maintenance treatment used to help keep airway inflammation under control (see, e.g., page 29), and that in spite of receiving regular inhaled corticosteroid (i.e., budesonide, beclomethasone diproprionate, or fluticasone propionate), the tested patients showed a reduction in sensitivity to formoterol that could be reversed only by use of other, systemic corticosteroids. According to Tan et al., the protection against down regulation of β2 adrenoreceptors conferred by systemic corticosteroid and the lack of such protection observed with inhaled corticosteroid "would suggest that a facilitatory effect of corticosteroid is conferred only with the systemic route" (page 34, col. 2, last full paragraph; emphasis added). Applicant fails to see in Tan et al. a motivation to instruct patients to use more inhaled budesonide as needed to prevent or treat acute episodes of asthma. To the contrary, Tan et al. teaches that one should instead use a systemically administered corticosteroid in order to achieve the desired results. By teaching that inhaled budesonide does not help in an acute attack, Tan et al. actually teaches away from the present invention. Furthermore, this reference certainly does not supply the teachings missing from Carling et al.

In light of the evidence presented above, Applicant maintains that claims 13-15, 17, 18, 20-36, 38 and 42 are not obvious over Carling et al., in view of Tan et al., and therefore requests the withdrawal of the rejection of the claims under 35 U.S.C. §103(a).

Claims 16-19 were rejected under 35 U.S.C. §103(a) as being unpatentable over Carling et al. in view of Tan et al., Aberg et al. and Ryrfeldt. Applicant maintains that for the reasons described above, independent claim 13, from which claims 16-19 depend, is nonobvious in view of the art cited by the Examiner. If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Applicant therefore requests that the rejection of claims 16-19 under 35 U.S.C. §103(a) be withdrawn.

Enclosed is Petition for Extension of Time for three months and a $980 check for the required fee. Any other charges or credits can be applied to Deposit Account No. 06-1050, with reference to Attorney Docket No. 06275-188001.

Respectfully submitted,

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